

REMARKS

Claims 1-5, 9, 23 and 27-37 are pending in this application. Entry of the remarks is respectfully requested.

I. Claims Rejections under 35 U.S.C. § 103

A. Claims 1, 9, 27-30 and 33-34 are Patentable over Omoigui in view of Muller *et al.*

Claims 1, 9, 27-30 and 33-34 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Omoigui (U.S. 2004/0038874, “Omoigui”) in view of Muller, *et al.* (U.S. 6,281,230, “Muller”) (Office Action, pages 2-3). Applicant respectfully disagrees.

The instant claims recite, *inter alia*, methods of treating complex regional pain syndrome (“CRPS”) using a specific dose of a specific compound, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione. The art cited by the Examiner does not teach or suggest the specific dose of the specific compound of the instant claims for treating CRPS. Omoigui teaches that pain of all kinds may be treated by mediating the inflammatory response with any of hundreds or thousands of drugs that may impact inflammation. Omoigui does not teach or suggest 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione. Muller teaches, *inter alia*, that certain isoindolines are TNF- α inhibitors. Included in the examples and claims of Muller is 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione. (Column 17, lines 26-29). Muller does not teach or suggest CRPS.

The Examiner alleges that the instant claims are obvious because Muller teaches that 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione is a TNF- α inhibitor, and Omoigui teaches that TNF- α inhibitors may be used to treat all diseases and disorders associated with pain, including CRPS. (Office Action, page 4). This conclusion is contrary to the law of obviousness. The mere “identification in the prior art of each component of [an invention] does not show that the combination as a whole...is obvious.” *Eli Lilly & Co. v. Zenith Goldline Pharmaceuticals, Inc.*, 471 F.3d 1369, 1379 (Fed. Cir. 2006). Instead, “the law requires a motivation to select the references and to combine them in the particular claimed manner to reach the claimed invention.” *Id.* (Emphasis added). In this case, the Examiner has provided no specific source of motivation to combine Omoigui and Muller in “the particular claimed

manner”— methods of treating CRPS using a specific dose of a specific compound, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione.

The mere fact that a species, CRPS in the instant case, is encompassed by a prior art genus, the disorders associated with pain disclosed in Omoigui, is not sufficient by itself to establish a *prima facie* case of obviousness. *See In re Baird*, 16 F.3d 380, 382, 29 U.S.P.Q.2d 1550, 1552 (Fed. Cir. 1994); *see also In re Brouwer*, 77 F.3d 422, 425, 37 U.S.P.Q.2d 1663, 1666 (Fed. Cir. 1996); MPEP § 2144.08. The Examiner has not provided any additional reason why one of ordinary skill in the art would select CRPS from Omoigui as the disease or disorder to be treated using a specific dose of a specific compound not taught or suggested therein. The mere fact that Muller teaches that the compound of the instant claims is a TNF- α inhibitor does not cure this defect. Thus, because Omoigui does not provide a “finite number of identified, predictable solutions,” but a “broad selection of compounds any of which could have been selected as the lead compound for further investigation...” the Examiner has failed to establish a *prima facie* case of obviousness. *Takeda Chemical Ind., Ltd. v. Alphapharm Pty., Ltd.*, 429 F.3d 1350, 1356, 1359 (Fed. Cir. 2007).

Further, as the Supreme Court explained in *KSR Int’l Co. v. Teleflex Inc.* 127 S.Ct. 1727 (2007), an obviousness determination takes into account whether the combination of elements would yield “anticipated success” or “predictable results.” *KSR*, 127 S.Ct. at 1739 and 1742. This principle has been applied repeatedly by the Federal Circuit post-*KSR* in cases regarding the pharmaceutical and biological arts. *See e.g. Takeda*, 429 F.3d at 1359; *Aventis Pharma Deutschland GmbH v. King Pharms, Inc.* 499 F.3d 1293, 1301 (Fed. Cir. 2007) (determination of obviousness based on whether the prior art provided an “expectation” that claimed compounds would have the intended properties.); *In re Trans Tex. Holdings Corp.*, 498 F.3d 1290 (Fed. Cir. 2007) (determination of obviousness for a patent relating to stem cell research based on whether the combination yielded “predictable results.”). Here, the Examiner has not demonstrated any sign of a “reasonable expectation of success” or “anticipated success” based on the broad disclosures of Omoigui and Muller, therefore, a *prima facie* case of obviousness cannot be made based on Omoigui and Muller alone.

B. Claims 1, 9, 27-30 and 33-34 are Patentable over Omoigui in view of Olmarker *et al.*

The Examiner has maintained the rejection of claims 1, 9, 27-30 and 33-34 under 35 U.S.C. § 103(a) as being unpatentable over Omoigui in view of Olmarker, *et al.* (WO 2002/080891, “Olmarker”) (Office Action, page 5). Applicant respectfully disagrees.

1. The Examiner has failed to demonstrate a motivation to combine, with reasonable expectation of success, the teachings of Omoigui and Olmarker.

Applicant maintains, as argued in the Response to the final Office Action dated September 10, 2007, that the methods of the instant claims are not obvious over Omoigui in view of Olmarker because neither reference teaches or suggests the compound of the instant claims for treating CRPS in the specific dose claimed.

The Examiner alleges that Omoigui teaches the use of “thalidomide analogs” for the treatment of persistent pain. (Office Action, page 6). First, Applicants again point out to the Examiner that Omoigui does not provide a definition for the term “thalidomide analogs.” Indeed, the only mention of thalidomide and analogs thereof is in paragraph [0023] of Omoigui, which is provided below in its entirety:

[0023] Thalidomide and analogues mainly inhibit tumor necrosis factor alpha (TNF-alpha) synthesis but the drugs also have effects on other cytokines. Thalidomides increase the production of the anti-inflammatory cytokine interleukin-10 (IL-10) in lesioned sciatic nerves. In addition, Thalidomides stimulate the release of the pain relieving natural opioid peptide methionine-enkephalin in the dorsal horn of the spinal cord.

Omoigui does not provide any structural description of “analog” of thalidomide. Without such description, one of ordinary skill in the art is unable to ascertain the scope of “thalidomide analogs” from Omoigui. Thus, Omoigui does not provide a “finite number of identified, predictable solutions,” but a “broad selection of compounds any of which could have been selected as the lead compound for further investigation.” *Takeda*, 429 F.3d at 1356, 1359. The necessary result is that the compound of the instant claims is not obvious from the teachings of Omoigui.

The Examiner responds to Applicant’s assertion that one of ordinary skill in the art would not be motivated to select a “thalidomide derivative” to treat CRPS from Omoigui by citing MPEP § 2123 and *In re Fulton*, 391 F.3d 1195 (Fed. Cir. 2004), for the proposition that “the mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives....” (Office Action, page 8).

Applicant does not dispute the fact that, in certain limited cases, a finite number of predictable solutions may lead to obvious combinations. *But see Takeda*, 429 F.3d at 1359 (nonobviousness found where the prior art does not provide a “finite number of identified, predictable solutions,” but a “broad selection of compounds any of which could have been selected as the lead compound for further investigation”). For example, in the case cited by the Examiner, the Court held that it was obvious to select a specific hexagon tread pattern on a shoe in view of prior art disclosure of square, circular, and even a slightly different hexagonal tread pattern. *In re Fulton*, 391 F.3d at 1197-1198. The alternatives in the prior art consisted of “cylindrical polygon shaped studs” that “provide sharp edges which bite into artificial turf for good traction.” *Id.* at 1201. However, this discrete set of alternatives cannot be said to be analogous to the selection of a specific chemical compound to treat a specific disease or disorder in a patient, much less the undefined scope of “thalidomide derivatives” recited in *Omoigui*. For this reason, it would not be obvious from the teachings of *Omoigui* to select the compound of the instant claims to treat CRPS, much less in the specific dosage claimed.

Olmarker does not cure the defects of *Omoigui*. As stated in Applicant’s previous Response, *Olmarker* merely teaches that TNF- α inhibitors may be used to treat low back pain. The specific compound of the instant claims is one of over eighty compounds and classes of compounds taught to be TNF- α inhibitors in *Olmarker*. CRPS is not taught or suggested in *Olmarker*, nor does *Olmarker* teach or suggest the use of the specific compound in specific amounts for treating CRPS as recited in the instant claims.

Furthermore, a *prima facie* case of obviousness cannot be made based on *Omoigui* and *Olmarker* alone because the Examiner has failed to show any “reasonable expectation of success” or “anticipated success” based on the broad disclosures of *Omoigui* and *Olmarker*. *See KSR*, 127 S.Ct. at 1739 and 1742; *Takeda*, 429 F.3d at 1359. The Examiner alleges that because *Olmarker* teaches that thalidomide derivatives inhibit TNF- α , one of ordinary skill in the art would expect “that they possess the same biological activity as thalidomide when used in the method of Omo[i]gui.” (Office Action, page 9). As discussed in Applicant’s previous response, the courts have long recognized the unpredictability of the biological properties of chemical compounds. *See In re Eli Lilly & Co.*, 902 F.2d. 943, 948 (Fed. Cir. 1990) (“we recognize and give weight to the unpredictability of

biological properties...”). Simply put, one of ordinary skill in the art would not reasonably expect that every “thalidomide analog” with TNF- α activity would be useful in treating CRPS. Without a more explicit teaching in the prior art of the instantly claimed method, one skilled in the art would have no motivation to test the specific compound of the instant claims over any other compound disclosed in Olmarker to treat each and every specific disorder related to pain in Omoigui. Furthermore, without additional guidance beyond Olmarker and Omoigui, one of ordinary skill in the art would have no reason to foresee that 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione would be effective in treating CRPS in the specific dose recited in the instant claims. Without such motivation, and without a reasonable expectation of success, a *prima facie* case of obviousness cannot be made. *KSR*, 127 S.Ct. at 1742; *Takeda*, 429 F.3d at 1359.

The Examiner further alleges that *Takeda* and *Grabiak* are inapplicable because “the present case does not involve the unsupported assertion that two compounds will function similarly based on structural similarity, but rather that these compounds qualify as “thalidomide analogs” under the definitions used by Omo[i]gui.” (Office Action, page 9). As discussed above, Omoigui does not provide a definition for the term “thalidomide analogs.” Moreover, the Examiner is indeed making the same assertion made in *Takeda* and *Grabiak*— that a compound of a given structure, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, has the same biological activity as a different, allegedly similar compound in a second reference, thalidomide. And as *Takeda* and *Grabiak* held, a *prima facie* case of obviousness “requires a showing of ‘adequate support in the prior art’ for the change in structure.” *Takeda*, 429 F.3d at 1356 (*quoting Grabiak*, 769 F.2d at 729). No such showing has been made.

Because the Examiner has not demonstrated that one skilled in the art would have had a motivation to combine, with reasonable expectation of success, the teachings of Omoigui and Olmarker, the Examiner has failed to state a *prima facie* case of obviousness. Therefore, the instant claims are not obvious over Omoigui in view of Olmarker.

2. Olmarker teaches away from the claimed dosage range.

Applicant again asserts that Olmarker teaches away from the claimed dosage range. Prior art is said to teach away from a claimed invention “[w]hen a piece of prior art ‘suggests that the line of development flowing from the reference’s

disclosure is unlikely to be productive of the result sought by the applicant....”
Medichem, 437 F.3d at 1165 (quoting *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)) (emphasis added); See also *KSR*, 127 S.Ct. at 1740 (citing *United States v. Adams*, 383 U.S. 39, 40 (1966)); MPEP § 2145 (citing *In re Grasselli*, 713 F.2d 731, 743, 218 U.S.P.Q. 769, 779 (Fed. Cir. 1983)). The Examiner states that the dosage ranges of Olmarker “are meant for oral administration” and that other methods of administration “would naturally require lower doses, such as those recited in the instant claims.” (Office Action, page 10). Regardless of whether other methods of administration would require lower doses than oral administration, Applicant respectfully points out that Olmarker teaches that a dosage of 200-800 mg is “more preferred,” and a dosage of 400-600 mg is “most preferred.” (page 11, line 30). With respect to the compound of the instant claims, Olmarker is silent as to lower dosage ranges for additional routes of administration. If one skilled in the art was motivated to select the specific compound of the instant claims from Olmarker, they would use the preferred dosages taught therein, not the much lower dosage of instant claim 1, and certainly not the even lower dosages of claim 35 (about 5 mg to 25 mg per day), claim 36 (about 10 mg per day) and claim 37 (about 5 mg per day). For these reasons, the dosage range disclosed by Olmarker for the specific compound of the instant claims teaches away from the dosages of the instant claims.

3. There are sufficient unexpected results to rebut even a *prima facie* case of obviousness.

Evidence of unexpected or superior results may be used to rebut a *prima facie* case of obviousness. *In re May*, 574 F.2d 1082, 1094 (C.C.P.A. 1978); see also *In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987); *Ortho-McNeil Pharmaceutical v. Mylan Laboratories*, 348 F. Supp. 2d 713, 755 (N.D. W. Va. 2004). Submitted herewith is a copy of G. Irving *et al.*, “A multicenter, open-label study to evaluate the safety and efficacy of lenalidomide (CC-5013) in the treatment of type-1 Complex Regional Pain Syndrome (CPRS).” Conference in the Mechanisms and Treatment of Neuropathic Pain, November 4-6, 2004, Bermuda (“Irving”), the reference provided with the previous Response. This reference demonstrates that 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, also known as lenalidomide or CC-5013, surprisingly showed significant efficacy and safety in treating complex regional pain syndrome in human patients. Therefore, the claimed method is a superior and

unexpectedly better method of treating complex regional pain syndrome than conventional therapies.

Irving provides the results of a clinical *in vivo* study of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione to evaluate the efficacy and safety of the claimed compound using adult humans with chronic, unilateral Type 1 complex regional pain syndrome. The results of the study showed that 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione unexpectedly provided significant reduction in pain in subjects nonresponsive to conventional therapy. Adverse events were mild and time-limited, indicating that the compound was surprisingly safe in human subjects.

In sum, the surprising efficacy and safety of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione in treating complex regional pain syndrome is sufficient to rebut even a *prima facie* case of obviousness. In view of these unexpected results, the instant claims are not obvious. *See In re May*, 574 F.2d at 1094. Therefore, Applicant respectfully requests that the rejection under 35 U.S.C. § 103(a) be withdrawn.


II. Conclusion.

In view of the foregoing, all the rejections of the claims should be withdrawn. Reconsideration, entry of the above remarks and allowance of the pending claims are respectfully requested. Should the Examiner not agree that all claims are allowable, a personal or telephonic interview is respectfully requested to discuss any remaining issues and to accelerate the allowance of the above-identified application.

A fee for an extension of time for a period of one month is required. The fee will be paid via EFS Web. The Commissioner is hereby authorized to charge any additional required fee under 37 C.F.R. § 1.17, or any other required fee, or any credits, to Jones Day Deposit Account No. 503013.

Respectfully submitted,

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